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The importance of low visfatin values in osteoid osteoma patient: a prospective study

S.A. ULUS, E. ÖZKUL

Department of Orthopedics and Traumatology, Dicle University Medical School, Diyarbakır, Turkey

Abstract. – OBJECTIVE: Visfatin is currently a cytokine that is extensively researched in the field of bone diseases. In this prospective study, we aimed to investigate the potential of serum visfatin levels as a biomarker for the diagnosis of osteoid osteoma.

PATIENTS AND METHODS: This study included a cohort of 20 patients diagnosed with osteoid osteoma (Group 1) and 30 healthy individuals (Group 2). The age, gender, cyst sizes, and visfatin values of all participants were documented and analyzed.

RESULTS: There was a significant difference in visfatin levels between the two groups. The median visfatin level in Group 1 was 6.13 ng/ml (IQR: 4.21-8.08), while in Group 2, it was 15.83 ng/ml (IQR: 11.11-20.6). The difference was statistically significant (p<0.000). The optimal cut-off value for visfatin was found to be 7.74 ng/ml, which had a 93% sensitivity and 78% specificity. An area under the curve of receiver operating characteristic (ROC) analysis of 0.85 indicates good diagnostic performance.

CONCLUSIONS: Our study revealed a significant decrease in visfatin levels among patients diagnosed with osteoid osteomas in comparison to the healthy control group. The ROC analysis revealed that visfatin exhibited a commendable diagnostic capacity, indicating its potential utility as a biomarker for osteoid osteoma.

Key Words:
Visfatin, Osteoid osteoma, Biomarker.

Introduction

Osteoid osteoma is a common benign neoplasm, accounting for up to 3% of primary bone tumors[1]. It predominantly affects young individuals[2,3], typically between the ages of 5 and 25. Despite the characteristic imaging appearance, diagnosing osteoid osteoma can be challenging due to its potential occurrence in any location within the skeleton[4]. Various bone lesions can mimic osteoid osteoma, presenting as small radiolucent lesions surrounded by a sclerotic rim[5]. Common differentials include bone infarction, chronic osteomyelitis, chondroblastoma, cortical desmoid, enchondroma, fibrous dysplasia, benign bone cysts, and subchondral cysts[6]. Less frequently encountered differentials include chondromyxoid fibroma, malignant tumors, eosinophilic granuloma, osteoblastoma, and rare infections[6]. Early diagnosis and treatment of osteoid osteoma are crucial for improving patients' quality of life, and avoiding unnecessary diagnostic procedures, treatments, and potential complications[7].

Visfatin, also known as Nicotinamide phosphoribosyltransferase (NAMPT), is considered to be a pleiotropic protein with many roles in physiology and pathology[8,9]. Visfatin is primarily produced by adipose tissue, although it is also synthesized by skeletal muscle, liver, immune cells, cardiomyocytes, and the brain, among other tissues. Visfatin has intrinsic NAMPT activity. Its intracellular form, called iNAMPT, controls the amounts of oxidized nicotinamide adenine dinucleotide (NAD) inside cells, while its extracellular form functions as a cytokine in response to inflammatory triggers or cellular stress. It participates in NAD synthesis and has been linked[10] to, among other things, the onset of obesity, insulin secretion, energy expenditure, cardiovascular function, homeostasis, lipid profile, and inflammation. Visfatin exhibits increased expression in several malignancies, including gastric, thyroid, urothelial, renal, cervical, oral, and cervical squamous cell carcinomas, rhabdomyosarcomas, and leiomyosarcomas[11-15]. Studies[16] have demonstrated that visfatin reaches higher levels in osteosarcoma and chondrosarcoma compared to benign bone tumors.

The promise and advantages of personalized medicine in providing treatment options that are better suited to each patient's genetic profile are widely acknowledged in the literature. Intensive information is a must in personalized medicine, whose ability to predict, diagnose, and treat patients depends on the high-dimensional data pro-

Corresponding Author: Sait Anıl Ulus, MD; e-mail: mdanilulus@gmail.com

duced by genetics and other technologies. This enables the execution of tailored cancer genomic analyses[17,18]. Malignant bone tumors are monitored, tumor aggressiveness is evaluated, and recurrence is tracked using a variety of signs. However, there is little research[19] on benign but aggressive tumors. To the best of our knowledge, visfatin levels have not yet been investigated in patients diagnosed with osteoid osteoma. In this study, we aimed to measure visfatin levels in patients with osteoid osteoma and investigate its potential as a diagnostic clue. Furthermore, the emergence of statistically significant results suggests that it may be worth exploring visfatin's role in pathogenesis in future studies.

Patients and Methods

Patients and Study Design

This is a prospective cross-sectional study, which included patients with osteoid osteoma admitted to the Faculty of Medicine's Orthopedics and Traumatology Clinic, Dicle University, Diyarbakır, between 15 January and 15 August 2023. Diagnosis of osteoid osteoma was confirmed through radiological imaging, medical history, and clinical findings. The study comprised 20 patients (Group 1) and a control group of 30 healthy individuals (Group 2). Patient group data included age, gender, tumor size, location, treatment type, follow-up duration, and recurrence. Patient identifiers were removed for data confidentiality. Age, gender, and serum visfatin levels were compared between the patient and control groups.

Collection and Preservation of Serum Specimens

Patients fasted for 8 hours before blood sample collection. A 5-cc blood sample was taken from the arm vein and transferred to sterile biochemistry tubes. The tubes were centrifuged at 5,000 rpm for 5 minutes to separate the serum. The serum was then transferred to Eppendorf tubes (Eppendorf, Hamburg, Germany) and stored at -80°C until analysis to preserve sample integrity was performed.

ELISA Assay of Visfatin in Serum

Serum samples were thawed to room temperature before analysis. The Enzyme-Linked Immunosorbent Assay (ELISA, Abbott Laboratories, IL, USA) technique was used to measure visfatin levels. A commercially available visfatin assay kit (Visfatin; Elabscience Biotechnology, Memorial Drive, Houston, USA. Catalog No.: E-EL-H1763) was employed following the manufacturer's instructions. BioTek ELx50 Microplate Washer and ELx800 Microplate Reader (BioTek Instruments, Inc. Santa Clara, California, USA) were used for the measurements. The microplate reader measured absorbance, proportional to visfatin concentration, while the microplate washer cleaned the wells. Visfatin levels in serum samples were determined based on ELISA readings, adhering to rigorous precision and accuracy standards.

Diagnostic Criteria for Osteoid Osteoma

Although there is no complete agreement on the diagnosis, the following are the most frequently used standards:

- The patient encounters sporadic, localized pain that worsens at night and can be alleviated with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).
- On a standard X-ray, the presence of an osteoid osteoma is indicated by a typically small, circular area of radiolucency known as a nidus, accompanied by surrounding sclerosis. This radiographic appearance supports the diagnosis of osteoid osteoma.
- A distinctive feature observed on a CT scan is a target-shaped nidus.
- A notable finding in three-phase bone scintigraphy is the "double density sign", which is typical of osteoid osteoma.

Inclusion Criteria

The study included individuals who were diagnosed with osteoid osteoma based on radiological imaging, medical history, and clinical findings that were consistent with osteoid osteoma. In addition to patients, healthy volunteers who willingly agreed to take part in the study were also included.

Exclusion Criteria

The study excluded patients who had previously undergone treatment for osteoid osteoma, those who presented with a recurrence of the condition, those whose pathology results were inconsistent with osteoid osteoma, and those who had metastatic bone disorders. Patients who smoke, consume heavy amounts of alcohol (more than 20 g of ethanol per week), and use steroids or estrogens were also excluded. The study excluded patients who had a chronic illness or an acute inflammatory condition that would have affected their serum

Table I. Patients' presenting symptoms.

Symptoms	N	%
Pain	18	90
Swelling	7	35
Synovitis findings	2	10

visfatin levels at the time of presentation. Patients who wanted to leave the study were also eliminated because this was a prospective study.

Statistical Analysis

The patient data underwent a comprehensive statistical analysis, including frequency evaluation, descriptive statistics (mean, standard deviation [SD], or median (interquartile range [IQR]), and analysis of various characteristics. Continuous data were expressed as mean±standard deviation. The normality of continuous variables' distribution was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov's tests. Student's *t*-test was used for normally distributed data, while non-parametric tests were employed for non-normally distributed data. Categorical variables were compared using the Chi-square test. Receiver operating characteristic curve (ROC) analysis was conducted for cut-off analysis. The correlation between visfatin levels and tumor size was assessed using the Spearman correlation test. Statistical analysis was performed using SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Two-sided *p*-values were reported, and statistical significance was defined as $p \leq 0.05$.

Results

Our study included a total of 50 participants, with 20 individuals in group 1 and 30 individuals in group 2. Among the study population, the most frequently reported symptom was pain, which was experienced by 90% of participants (n=18). Swelling was the second most prevalent complaint, reported by 35% of participants (n=7). In contrast, the occurrence of synovitis findings was relatively rare, reported by only two participants, representing 10% of the total group (Table I).

The median age of the participants in our study was 19 (IQR: 18-21) years. The majority of the cohort (54%, 27 participants) were males. The participants' tumor nidus sizes varied, with a median value of 7.5 (IQR: 5-8.75) mm. The majority of tumor localizations, or 45% (n=9) of cases, were discovered in the femur. The tibia (n=8) followed at 40%, the humerus (n=2) at 10%, and the hand (n=1) at 5%. Various therapeutic modalities were used. Most significantly, curettage was the most common form of treatment, used in 50% (n=10) of patients. 40% (n=8) of patients received radiofrequency ablation, another widely utilized procedure. 10% (n=2) of patients underwent excision under CT supervision. The average follow-up time was 12.4 (±3.5) months. In this time frame, 10% (n=2) of our research participants experienced recurrences (Table II).

Group 1 median age was 17.5 years (IQR: 14.75-21.25), whereas Group 2's was 19 years (IQR: 18-21). Statistically, there was no age difference between the two groups (p=0.399). 60% (n=12) of members in Group 1 were male, compared to 54% (n=16) of Group 2 members (p=0.813). However, there was a significant difference in visfatin levels between the two groups. The median visfatin level in Group 1 was 6.13 (IQR: 4.21-8.08) ng/ml, while in Group 2, it was 15.83 (IQR: 11.11-20.6) ng/ml. The difference was statistically significant (p<0.000; Table III).

A ROC analysis was carried out to establish the diagnostic utility of visfatin in osteoid osteoma. The area under the curve (AUC) value of 0.85 indicated good diagnostic performance. The optimal cut-off value for visfatin was found to be 7.74 ng/ml, which had a 93% sensitivity and 78% specificity (Figure 1).

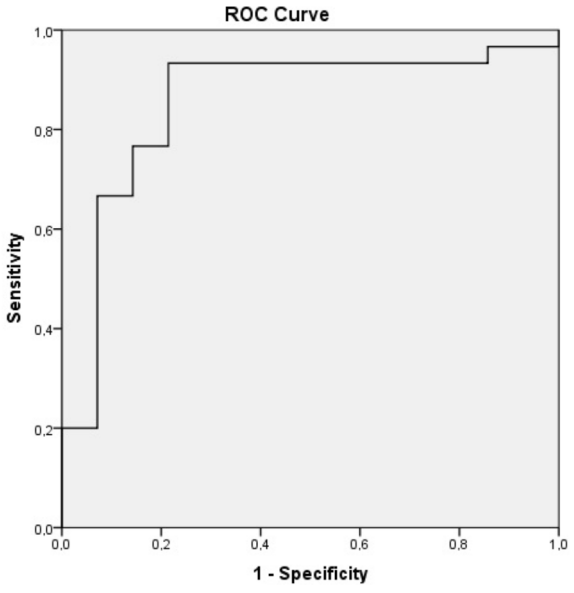

Figure 1. ROC analysis for visfatin levels in osteoid osteoma.

Table II. Overall observations of the study participants.

	N (%)
Age*	19 (18-21)
Gender (Male)	27 (54%)
Tumor nidus size (mm)*	7.5 (5-8.75)
Tumor localization	
Femur	9 (45%)
Tibia	8 (40%)
Humerus	2 (15%)
Hand	1 (10%)
Treatment	
Curettage	10 (50%)
Radiofrequency	8 (40%)
CT-guided excision	2 (10%)
Follow-up#	12.4 (±3.5)
Recurrence	2 (10%)

*Median (IQR); #Mean, SD.

Discussion

To the best of our knowledge, this study represents the first attempt to explore the significance of serum visfatin levels as a diagnostic tool and potential contributor to the pathogenesis of osteoid osteoma. Our findings demonstrate a significant reduction in serum visfatin levels among patients with osteoid osteoma in comparison to healthy control subjects. This observation may provide initial evidence indicating the potential involvement of visfatin in the underlying mechanisms of osteoid osteoma.

Visfatin, a 52 kDa protein, exhibits a broad expression throughout the musculoskeletal system, encompassing muscle, bone, synovium, and cartilage[15,20]. Visfatin serum levels were positively connected with increased expression of pro-inflammatory factors, such as IL-6, tumor necrosis factor (TNF), and C-reactive protein (CRP), according to liquid biopsy examination of individuals from various backgrounds. Interleukin 1 (IL-1), TNF, and IL-6 were increased by visfatin in human leucocytes and monocytes, confirming this association. Additionally, *in-vivo* models[21] supported the finding that inflammatory settings were linked to greater circulating levels of visfatin. Visfatin treatment was shown to increase the levels of IL-6 in the blood of mice[21]. However, the capacity of visfatin and important inflammatory molecules like IL-6, IL-1, TNF, and TLR4 agonists to establish a positive feedback loop further supported the association between visfatin and inflammation[21]. It is recognized as a significant pro-inflammatory mediator, and its circulating concentrations have been extensively investigated in diverse contexts such as cancer, metabolic disorders, and chronic inflammatory conditions. Moreover, visfatin has emerged as a potential biomarker in various pathological states. Notably, elevated levels of circulating visfatin have been reported in rheumatoid arthritis[22], osteoarthritis[23], and osteoporosis[24] when compared to individuals without these conditions.

Serum visfatin levels are also influenced by other processes. It is known that serum visfatin concentrations in healthy individuals may be associated with body weight. Dietary changes such as inadequate nutrition, overeating, and exercise have significant effects on adipose tissue metabolism, which can also impact visfatin concentrations. Kidney function, lipid metabolism, and inflammation can also influence serum visfatin levels[25].

In our study, Group 1 had a median visfatin level of 6.13 ng/ml (IQR: 4.21-8.08), while Group 2 had a median level of 15.83 ng/ml (IQR: 11.11-20.6). Significantly lower levels of visfatin were observed in patients diagnosed with osteoid osteoma when compared to the control group, with the observed difference reaching statistical significance ($p<0.000$). Visfatin and nidus size were not correlated ($p>0.05$).

In a study conducted by Wang et al[26] in 2022, it was observed that patients with non-traumatic femoral head avascular necrosis had significantly lower serum visfatin levels compared to the control group. Furthermore, they reported a negative correlation between visfatin levels and the stage of the disease. Based on these findings, the

Table III. Comparative analysis of variables between groups.

	Group 1 (n=20)	Group 2 (n=30)	*p*-value
Age*	17.50 (14.75-21.25)	19 (18-21)	0.399
Gender (male)#	12 (60%)	15 (50%)	0.813
Visfatin levels* ng/ml	6.13 (4.21-8.08)	15.83 (11.11-20.6)	**<0.000**

*Median (IQR), #N (%).

authors suggested that visfatin could serve as a potential biomarker for early diagnosis and prediction of disease severity.

Regarding multiple myeloma, a study by Venkateshaiah et al[27] demonstrated that inhibiting visfatin could reduce bone lesions and osteoclastic activity in patients with this condition.

Osteoid osteoma and osteoblastoma are morphologically similar bone-forming tumors, which is why osteosarcoma and osteoblastoma can sometimes be indistinguishable histologically. It has been noted[28] that osteoblastomas and osteoid osteomas exhibit high levels of FOS/FOSB gene expression, which supports their diagnosis.

In the context of other bone-related diseases, such as osteosarcoma, chondrosarcoma, and giant cell tumors, investigations into visfatin levels have revealed increased expression compared to normal bone and cartilage. Notably, in chondrosarcoma, a correlation between visfatin expression and disease stage has been identified[15]. A meta-analysis by Mohammadi et al[20] has indicated that altered visfatin expression is a potential indicator of poor clinical outcomes in tumor patients.

Osteoid osteoma commonly presents with symptoms that resemble rheumatological diseases, particularly when located in the periarticular region, leading to potential misdiagnoses that mimic arthritis[29]. In a study by Traore et al[30], cases of intraarticular osteoid osteomas in children were described, which were initially misdiagnosed as juvenile idiopathic arthritis and subsequently treated with intraarticular corticosteroid injections. However, we know that visfatin is elevated in most rheumatological diseases[31-36], whereas, in our study, visfatin was found to be low.

Limitations and Strengths

One of the primary limitations of our study is the small sample size. However, if similar studies with larger sample sizes corroborate these results, they may provide valuable insights into the differential diagnosis between rheumatological diseases and bone neoplasms.

The ROC curve analysis conducted in our study to assess the diagnostic potential of serum visfatin levels for osteoid osteoma demonstrated relatively high diagnostic efficacy, as indicated by an AUC of 0.85. Using a cut-off value of 7.74 ng/mL, the sensitivity of visfatin in detecting osteoid osteoma was determined to be 93%, while the specificity was calculated to be 78%. These findings strongly indicate that serum visfatin has the potential to serve as a valuable biomarker in the investigation of both the differential diagnosis and pathogenesis of osteoid osteoma.

While our study provides insights into the potential use of visfatin as a diagnostic biomarker for osteoid osteoma, it has several limitations:

- The sample size was small, limiting the generalizability of the findings. Conducting larger-scale studies is necessary for validation.
- Additionally, being a single-center study introduces selection bias and restricts generalizability. Multi-center studies are needed to confirm the results in diverse populations.
- Cross-sectional design limits establishing causal relationships or observing changes over time. Longitudinal studies would provide more robust evidence. Our study focused exclusively on visfatin and did not explore other potential biomarkers, which may improve diagnostic accuracy. Furthermore, although known factors affecting visfatin levels were excluded, other confounding factors may exist, introducing potential bias.

This study has also notable strengths that enhance its significance and impact:

- It is the first study to investigate serum visfatin levels as a diagnostic tool for osteoid osteoma, stimulating further research into visfatin and other potential biomarkers in its diagnosis.
- The study design was prospective and cross-sectional, ensuring an unbiased selection of patients and controls.
- Rigorous methods were employed for sample collection and analysis, using the reliable ELISA technique.
- Comprehensive statistical analysis, including receiver operating characteristic curve (ROC) analysis, determined the optimal cut-off value for diagnosing osteoid osteoma based on visfatin levels.
- Well-defined inclusion and exclusion criteria ensured a representative study population of osteoid osteoma patients.

Conclusions

In individuals diagnosed with osteoid osteoma, there was a notable decrease in serum visfatin levels compared to healthy subjects. The ROC analysis revealed that visfatin exhibited a com-

mendable diagnostic capacity, indicating its potential utility as a biomarker for osteoid osteoma. However, further comprehensive investigations are warranted to expand and enhance the general understanding of this relationship.

Conflict of Interest
The authors declare that they have no conflict of interests.

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None.

Ethics Approval
Ethical approval for this study was obtained from the Ethics Committee of the Medical Faculty of Dicle University (Number: 235-2023).

Informed Consent
The protocol was performed in accordance with the Declaration of Helsinki, and the participants or their families provided written informed consent.

Authors' Contributions
Both authors equally contributed to and approved the final version of the paper.

Data Availability
All data associated with this paper are available from the corresponding author upon reasonable request.

ORCID ID
Sait Anıl Ulus: 0000-0003-3270-1648
Emin Özkul: 0000-0003-2149-8154.

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